REMARKS

Status of Claims and Amendment

Claims 1, 3-12, 14-17, 19-23, 26 and 27 are pending in the application. Claims 1, 3-12, 14-17, 19-23, 26 and 27 are rejected. Claims 1-27 are canceled herewith without prejudice or disclaimer. Claims 28-38 are newly added.

Support for new claims 28-38 may be found in the original claims and throughout the specification. For example, page 3, last full paragraph to page 4, line 24 and lines 28-34, page 5, line 8 and last two paragraphs, page 6, lines 16-18 and last two paragraphs, Chemical Example 1 at page 7, and Example 1 at pages 10-14 of the specification.

No new matter is added.

Response to Rejection Under 35 U.S.C. § 112 for Enablement

On pages 2-5 of the Office Action, claims 26-27 are rejected under 35 U.S.C. § 112, first paragraph, because the specification, while being enabling for the treatment of osteoarthritis, allegedly does not provide enablement for the prophylaxis of osteoarthritis and one of ordinary skill in the art would have to perform additional experimentation with different sulfated polysaccharides using healthy mammals, in order to determine the preventive efficacy of the instant active agents.

Claims 26-27 have been canceled without prejudice. Accordingly, the rejection is rendered moot with regard to claims 26-27.

Nevertheless, and solely to advance prosecution of the present application, new claims 28-38 have been added that meet the enablement requirements because the claims are directed to a method for the treatment of osteoarthritis, which the Office Action acknowledges is enabled by the specification.

Further, with regard to the Office Action's statements that WO03/006645 teaches treatment of osteoarthritis, rheumatoid arthritis, and other anti-inflammatory conditions, Applicants note that the term "osteoarthritis" is not disclosed anywhere throughout WO03/006645. WO03/006645 relates to method of inhibiting heparanase activity and treating various conditions by administering to an animal an effective amount of an immunogen that illicits an immune response to heparanase (see Abstract). For example, the methods of WO03/006645 are used to treat conditions relating to injury, inflammation, diabetes, or autoimmunity. Further, the methods are used to treat an angiogenic condition such as artherosclerosis, arthritis, macular degeneration, and psoriasis (see paragraph [49] on pages 17-18 and claims 13-15).

In addition, although the Office Action states that the Merck Manual teaches that the etiology of osteoarthritis is unknown and appears to be a complex set of interactions, Applicants note that page 1340 of the Merck Manual states "[i]initially, osteoarthritis is noninflammatory." This supports the description provided in Martindale, The Extra Pharmacopoeia cited in the previous response.

Response to Rejection Under 35 U.S.C. § 112 for Indefiniteness

On page 5 of the Office Action, claim 23 is rejected under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite.

The phrase, "whose structure is derived from a sulfated polysaccharide" followed by Markush members allegedly is unclear because the derivatives of the sulfated polysaccharides are not defined.

In response, and solely to advance prosecution of the present application, claim 23 has been canceled. Accordingly, the rejection is rendered moot.

Further, the alleged indefinite language is not in the newly added claims.

Response to Rejection Under 35 U.S.C. § 103

On page 7 of the Office Action, claims 1, 3-12, 14-17, 19-23 and 26-27 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Cullis-Hill *et al.* (U.S. Patent No. 5,145,841) in view of Komai *et al.* (International Journal of Biological Macromolecules, 2002, 30, 197-204), Dictionary.com (2002, page 3) and Martindale: The Extra Pharmacopoeia 1996, page 11.

Hill is asserted for the reasons of record. In addition, the Office Action appears to assert that Hill teaches that the sodium salt of polysulfated xyloside is an inhibitor of PMN elastase and other enzymes that degrade connective tissue and articular cartilage so that polysulfated xyloside binding to articular cartilage and connective tissues promotes joint hyaluronate and articular cartilage. The Office Action asserts that Hill discloses that the polysulfated polysaccharides abbreviated as SP 54 and Arteparon have a sulfur content of about 16% and 13% respectively. The Office Action further asserts that even though this degree of sulfation taught by Hill is argued to be lower than the claimed degree of sulphation, one of ordinary skill in the art would have known to adjust the degree of sulphation in order to achieve optimal beneficial effects.

Komai is asserted for the reasons of record, i.e., for teaching the use of gellan sulfate to provide therapeutic benefits to patients with rheumatoid arthritis. The Office Action acknowledges that Komai does not specifically teach or exemplify the use of gellan sulfate for the treatment of osteoarthritis.

Dictionary.com is asserted for the reasons of record, i.e., to teach that both rheumatoid arthritis and osteoarthritis involve degradation of bone joints.

Martindale is asserted to teach that osteoarthritis and rheumatoid arthritis are characterized by degradation/destruction of cartilage.

The Office Action asserts that because the polysulfated xyloside of Hill binds to articular cartilage and connective tissues to promote joint hyaluronate and articular cartilage, gellan sulfate would also be expected to bind to the articular cartilage and connective tissues and perform the same function. The Office Action asserts that one of skill in the art would be motivated to use the active agents in the method of treatment as instantly claimed since the agents inhibit the release and action of serine proteinases. The Office Action appears to assert that since proteoglycans confer resilience to the joints, and are degraded by proteinases, inhibiting the release of and action of proteinases prevents the depletion of the proteoglycans to maintain the resilience of joints. In this regard, the Office Action asserts that one of skill in the art would expect structurally related polysulfate polysaccharides to perform the same functions and to be useful in the claimed method of treatment. Thus, the Office Action concludes that it would have been obvious to one of ordinary skill in the art at the time the invention was made to use polysulfated polysaccharides used for treating rheumatoid arthritis to also treat osteoarthritis as claimed, since osteoarthritis and rheumatoid arthritis are characterized by degradation/destruction of cartilage.

Applicant's arguments that (1) osteoarthritis (degenerative joint disease) and rheumatoid arthritis (inflammatory disease) are different despite synovial inflammation observed in advanced osteoarthritis; (2) Hill teaches away from the claimed invention because Hill uses metallic complexes of polysulfated polysaccharides[1]; and (3) neither Hill nor Komai teaches or

[1] With regard to this aspect of Applicants' arguments, the Office Action asserts that the disclosure in Hill teaching that metallic complexes alters the conformation and rigidity of the polysaccharide chain to its biological activity is not a teaching away from the instant invention because Hill does not specifically teach that the presence of the metal destroys its biological activity. The Office Action appears to assert that "influencing" is not interpreted by one of ordinary skill in the art as teaching …(footnote continued)

suggests oral administration, were not found to be persuasive. The Office Action asserts that even though rheumatoid arthritis may have an immunological component, both rheumatoid arthritis and osteoarthritis have joint and cartilage degradation/destruction. For the reasons discussed above, sulfated polysaccharides are asserted to inhibit enzymes that are responsible for such degradation. Accordingly, the Office Action asserts that Applicants have not shown how rheumatoid arthritis and osteoarthritis are different and why the same treatment will not work for both.

Initially, Applicants note that claims 1, 3-12, 14-17, 19-23 and 26-27 have been canceled without prejudice. Accordingly, the rejection is rendered moot with respect to claims 1, 3-12, 14-17, 19-23 and 26-27.

Furthermore, Applicants note that new claims 28-38 are not rendered obvious by Hill, Komai, Dictionary.com, and Martindale for at least the following reasons.

First, with regard to the Office Action's assertions that Applicants have not shown how osteoarthritis is different from rheumatoid arthritis so that the same treatment would not work for both, Applicants respectfully direct the Examiner's attention to the following evidence to demonstrate that <u>treatments for osteoarthritis are different from treatments for rheumatoid arthritis</u>.

<u>The following drugs discussed below are indicated for the treatment of rheumatoid arthritis, but not for the treatment of osteoarthritis</u>.

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away from the instant invention especially when Hill teaches that such complexes are useful for treating both osteoarthritis and rheumatoid arthritis using animal models.

The pharmacological treatment for rheumatoid arthritis generally includes two groups of drugs: drugs indicated to relieve the symptoms of the disease such as pain (e.g., NSAIDs, Coxibs, glucocorticoides) and disease modifying drugs (e.g., Disease Modifying AntiRheumatic Drugs; hereinafter "DMARDs"). In addition, biological agents have also been used recently in the treatment of rheumatoid arthritis, such as drugs modulating specifically white blood cells and tumour necrosis factor ("TNF") blockers.

a) DMARDs for Rheumatoid Arthritis

DMARDs are drugs indicated for the treatment of certain types of inflammatory arthritis such as rheumatoid arthritis, psoriatic arthritis and ankylosing spondylitis. Traditionally, DMARDs have been used to treat other diseases such as certain types of cancer, IBD (Inflammatory Bowel Diseases) and organ transplant rejections (see Fries *et al.* submitted herewith[2]).

According to the European League Against Rheumatism (EULAR) for the management of rheumatoid arthritis (see Combe *et al.* previously submitted in IDS filed February 12, 2007), the patients who present indications of erosive or persistent arthritis must begin pharmacological treatment with DMARDs, such as, methotrexate as a first line treatment, and then sulfasalazine and leflunomide as alternative lines of treatment. It has unequivocally been shown that DMARD therapy early in the course of rheumatoid arthritis retards progression of damage and disability to a larger degree compared with delayed institution (see Smolen *et al.* submitted herewith, and Combe *et al.*).

[2] In accordance with M.P.E.P. § 609.05(c), the documents cited herein in support of Applicants' remarks are being submitted as evidence directed to an issue raised in the Official Action, and no fee pursuant to 37 C.F.R. 1.97 or 1.98, or citation on a FORM PTO/SB/08A & B is believed to be necessary.

In contrast, none of the three above-indicated medicines, i.e., methotrexate, sulfasalazine, and leflunomide, indicated for the treatment of rheumatoid arthritis is mentioned in the recommendations by the European League Against Rheumatism (EULAR) for treatment of knee osteoarthritis (see Jordan *et al.* previously submitted in IDS filed February 12, 2007).

For example, as discussed above, methotrexate (Rheumatrex®) is indicated for the treatment of rheumatoid arthritis, among other inflammatory pathologies (see Visser *et al.* submitted herewith). However, methotrexate is not prescribed for the treatment of osteoarthritis (see Rheumatology Therapeutics: Drugs and Biologics[3], submitted herewith, and Jordan et al.).

b) Biological agents:

1. White blood cell specific modulators

White blood cell specific modulators control inflammation in an effective way and include:

- Abatacept (Orencia): subcutaneous or intravenous administration once a month. It reduces the number of T-cells (a type of white blood cell).

- Rituximab (Rituxan), subcutaneous or intravenous administration twice a year. It reduces the number of B cells (a type of white blood cell).

[3] It is noted that aspirin, celecoxib, methylprednisolone, and non-selective NSAIDs and triamcinolone are indicated for use with rheumatoid arthritis and osteoarthritis. These drugs are antiinflammatories and analgesics and are believed to be used for management of pain symptoms. However, as previously argued, although there may be synovial inflammation observed with advanced osteoarthritis, it is well recognized in the art that such inflammation is different in nature to that observed with rheumatoid arthritis. (See page 11, 2nd column, 1st paragraph under "Osteoarthritis" in Martindale - The Extra Pharmacopoeia). Accordingly, the required treatment therapies for the underlying cause of osteoarthritis and rheumatoid arthritis are different.

2. Tumour necrosis factor blockers (TNF)

Tumour necrosis factor blockers are a relatively new type of drugs which block a protein in the body involved in the production of inflammation. They are administered intravenously and comprise:

- Adalimumab (Humira)

- Etanercept (Enbrel)

- Infliximab (Remicade)

None of these biological agents is prescribed for the treatment of osteoarthritis (see Jordan et al. and Rheumatology Therapeutics: Drugs and Biologics).

In contrast, the following drugs discussed below are indicated for the treatment of osteoarthritis, but not for the treatment of rheumatoid arthritis:

Drugs indicated for the treatment of osteoarthritis are, for example, the SYSADOAs (*Symptomatic Slow Acting Drug for Osteoarthritis*): chondroitin sulfate, glucosamine, hyaluronic acid and diacerein (see Jordan *et al.* and Rheumatology Therapeutics: Drugs and Biologics).

On the other hand, although therapies exist to retard the progression of rheumatoid arthritis with disease-modifying agents, comparable agents for the treatment of osteoarthritis have not been found that would be as efficient as the ones indicated for the treatment of rheumatoid arthritis (see Fox *et al.*, submitted herewith).

Accordingly, the treatment of rheumatoid arthritis and osteoarthritis are clearly delineated in the medical art, and each respective treatment is directed toward the etiology or cause of the disease. That is, the treatments for rheumatoid arthritis are directed towards the inflammation that is the basis of rheumatoid arthritis, and the treatments for osteoarthritis are directed towards

slowing the progression of articular cartilage loss and marginal and central new bone formation that is the basis of osteoarthritis.

Hill does not teach or suggest the presently claimed inulin sulphate or inulin polysulfate

As previously acknowledged by the Office Action, "Hill does not exemplify the treatment of osteoarthritis using the polysulfated polysaccharides as instantly claimed" (see page 8 of Office Action mailed October 27, 2008). Also, Hill does not teach or suggest the presently claimed inulin sulphate or inulin polysulphate because the polysulphated polysaccharides disclosed in Hill are dextran, xylan, chondroitin, dermatan and hyaluronic acid (see column 9, lines 51-54).

Hill teaches away from administration of the presently claimed inulin sulphate or inulin polysulfate for treatment of osteoarthritis

As previously argued, Hill describes the treatment of osteoarthritis with "metallo complexes of polysulphated polysaccharides". Hill teaches away from (1) using inulin sulphate or inulin polysulphate because such compounds would not "have the utility found by the present inventors [of Hill]" (see column 10, lines 38-53 of Hill), and (2) using inulin sulphate or inulin polysulphate in acid form or as an alkaline metal salt or alkaline earth metal salt as presently claimed. For instance, with regard to (2) Hill explicitly teaches that "*the metallo complexes of this class of drugs (polysulphated polysaccharides) were more potent stimulators of proteoglycan synthesis than the sodium salt*" (see column 24, lines 1-5 of Hill). Also, Hill teaches away from using other known salts of inulin sulphate or inulin polysulphate like sodium, potassium, or ammonium, because Hill considers that "*the formation of these metallo-polysulphated polysaccharide complexes provides a useful means of transporting selected metals into bodily tissues, since unlike the known salts of the polysulphated polysaccharides like*

sodium, potassium, or ammonium, which dissociate into the respective ions when dissolved in water, the complexes of the present invention do not dissociate in an aqueous or physiological media" (see column 11, lines 49-59 of Hill).

The Office Action on page 7 asserts that Hill teaches that "the said sulphated polysaccharides can also be used as their salts (Co1. 9, lines 55-58)". Applicants note that no such statement is found at column 9, lines 55-58 of Hill. Nevertheless, Applicants disagree with the interpretation of the paragraph at column 9, lines 55-58 of Hill by the Examiner because column 9, lines 55-58 of Hill describes the effective metallo-polysulphated complexes formed between the polysulphated polysaccharides "selected from the group consisting of dextran, xylan, chondroitin, dermatan and hyaluronic acid" at lines 53-54 of column 9 and the multivalent metal ions Ag+ and Au+ and quaternary ammonium compound complexes disclosed at lines 557-58 of column 9. Accordingly, when Hill describes that *"[t]he effective complexes are those formed between the aforementioned polysulphated polysaccharides and multivalent metal ions, Ag+ and Au+, and quaternary ammonium compound complexes*", Hill is referencing the metallo-complexes, not the salts.

Hill does not teach or suggest oral administration of inulin sulfate or inulin polysulfate for treatment of osteoarthritis as presently claimed

Hill does not disclose oral administration of the presently claimed inulin sulfate or inulin polysulfate. As previously argued, the μg/ml unit doses disclosed in Hill are based upon *in vitro* treatment of cells in tissue culture. Also, although Hill discloses doses for intra-articular administration of hydrocortisone and pentosan polysulphate (see column 8, lines 28-45 and Table 1 of Hill), such doses are based upon intra-articular injection to a rabbit, and are given in combination with a glucocorticoid to prevent the loss of proteoglycans from joints induced by

weekely intra-articular administration of the polysulphated polysaccharides listed in Table 1 of Hill. (See column 8, lines 28-45 of Hill).

The presently claimed inulin sulfate or inulin polysulfate has unexpectedly superior effectiveness in treating osteoarthritis

The Office Action states on page 7 that "according to Hill the sodium salt of polysulphated xyloside is an inhibitor of PMN elastase and other enzymes that degrade connective tissue and articular cartilage". Applicants note that as discussed in the documents listed below (previously submitted with Amendment filed on January 27, 2009), sulfated glycosaminglycan (namely chondroitin sulphate), as well as the glycosaminglycan without any sulfate groups (namely hyaluronic acid), inhibit the synthesis of metalloproteinases and consequently are useful in the treatment of osteoarthritis.

- J. Monfort *et al.* Drugs Exptl. Clin. Res.,)00a(2), 71-76 (2005);

- M.W. Orth *et al.* Equine vet. J., Suppl., 34, 224-229 (2002);

- A. Sasaki *et al.* Tohoku J. Exp. Med., 204, 99-107 (2004); and

- K. Takahashi *et al. Osteoarthritis and Cartilage*, 7, 182-190 (1999)),

Although sodium salts of some polysaccharides, sulphated or not sulphated, are known for the treatment of osteoarthritis, the present inventors have surprisingly found that orally administered inulin polysulphate sodium salt of the present invention has unexpectedly superior effectiveness for the treatment of osteoarthritis in comparison to orally administered chondroitin sulphate sodium salt at the same dose (see *in vivo* assay in Rule 132 Declaration submitted January 27, 2009). This demonstrates that it was not to be expected that all sulphated polysaccharides would have the same effectiveness for the treatment of osteoarthritis when administered orally.

Komai is evidence that the treatment therapies for osteoarthritis and rheumatoid arthritis are different

As discussed above, Applicants have provided evidence that osteoarthritis and rheumatoid arthritis are different diseases, which require different treatment therapies. Komai is further evidence that the required therapies for osteoarthritis and for rheumatoid arthritis would be different. As previously argued, Komai describes "a plasma-separation bilayer gellan-gallansulfate adsorbed for direct removal of extra domain A containing fibronectin from the blood of rheumatoid arthritis patients." Accordingly, Komai does not cure the deficiencies of Hill because Komai is merely asserted to teach a connection between gellan sulfate and rheumatoid arthritis. However, because Hill explicitly discloses the use of metallo complexes of polysulphated polysaccharides *instead* of polysulphated polysaccharides or a pharmaceutically acceptable salts of polysulphated polysaccharides, Hill *teaches away* from modifying its teachings with the gellan sulphate of Komai. In fact, based upon the disclosure in Hill, one of ordinary skill in the art would have been *discouraged* from modifying the teachings of Hill with the teachings of Komai.

Thus, the combination of Hill and Komai do not teach or suggest the presently claimed method for treatment of osteoarthritis.

Reconsideration and withdrawal of the rejection under § 103(a) is respectfully requested.

Conclusion

In view of the above, reconsideration and allowance of this application are now believed to be in order, and such actions are hereby solicited. If any points remain in issue which the Examiner feels may be best resolved through a personal or telephone interview, the Examiner is kindly requested to contact the undersigned at the telephone number listed below.

The USPTO is directed and authorized to charge all required fees, except for the Issue Fee and the Publication Fee, to Deposit Account No. 19-4880. Please also credit any overpayments to said Deposit Account.

Respectfully submitted,

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